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09/491,896	01/24/2000	Matthew J. During	102194-6	9210

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BUNNER, BRIDGET E

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Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary

Offic Action Summary	Application No.	Applicant(s)
	09/491,896	DURING, MATTHEW J.
	Examiner Bridget E. Bunner	Art Unit 1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 28 January 2002.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-44,47-72 and 74-108 is/are pending in the application.
- 4a) Of the above claim(s) 4,13-21,33-35,47-53,55-58,62-67,69 and 77-85 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-3,5-12,22-32,36-44,54,59-61,68,70-72,74-76 and 86-108 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) 1-44,47-72 and 74-108 are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) Interview Summary (PTO-413) Paper No(s) _____.
5) Notice of Informal Patent Application (PTO-152)
6) Other: _____

DETAILED ACTION

Continued Prosecution Application

The Request for Continued Examination (RCE) filed on 28 January 2002 (Paper No. 14) under 37 CFR 1.114 based on parent Application No. 09/491,896 is acceptable and an RCE has been established. An action on the RCE follows.

Status of Application, Amendments and/or Claims

The amendment of 28 January 2002 (Paper No. 15) has been entered in full. Claims 45-46 are cancelled, claims 1, 8-9, 22, 29, 41, 54, 59, 70, and 74 are amended, and claims 86-108 are added.

This application contains claims 4, 13-21, 33-35, 47-53, 55-58, 62-67, 69 and 77-85 drawn to an invention nonelected with traverse in Paper No. 8 (06 December 2000). A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-3, 5-12, 22-32, 36-44, 54, 59-61, 68, 70-72, 74-76, and 86-108 are under consideration in the instant application and read upon the elected invention of administration of an amino acid vaccine comprising an antigen wherein the antigen elicits the production of antibodies. This method was elected with traverse in Paper No. 8 (06 December 2000).

Withdrawn Objections and/or Rejections

1. The rejection of claims 9, 29, 41, and 59 under 35 U.S.C. § 112, second paragraph at pg 9-10 of the previous Office Action (Paper No. 12, 27 August 2001) are *withdrawn* in view of the amended claims (Paper No. 15, 28 January 2002).

Drawings

2. The formal drawings submitted 18 June 2001 will be forwarded to the draftsperson for review at the time of allowance.

Specification

The disclosure is objected to because of the following informalities:

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "NMDAR1 VACCINE AND MODIFICATION OF A TARGET RECEPTOR BY ADMINISTRATION OF THE VACCINE".

Appropriate correction is required.

Claim Objections

4. Claims 1-3, 5-12, 22-32, 36-44, 54, 59-61, 68, 70-72, 74-76, and 86-108 are objected to because of the following informalities:

- 4a. Claims 1-3, 5-12, 22-32, 36-44, 54, 59-61, 68, 70-72, 74-76, and 86-108 recite a non-elected group. Specifically, the claims recite administering a composition comprising an isolated antibody.
- 4b. Claims 3, 6-8, 24-28, 38-40, 68, 72, 75-76, and 88 recite non-elected species of disorders and type of target protein/antigen.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph

5. Claims 1-3, 5-12, 22-32, 36-44, 54, 59-61, 68, 70-72, 74-76, and 86-108 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-3, 5-12, 22-32, 36-44, 54, 59-61, 68, and 86-108 recite a method for modifying the function of a target receptor associated with a neurological disorder in a subject, a method for modifying the function of a target receptor associated with a neurological disorder in the central nervous system of a subject, a method for modifying the function of a target receptor associated with cognition in the central nervous system of a subject, a method for modifying the function of a target receptor associated with a neuroendocrine disorder in the central nervous system of a subject, a method for modifying the function of an N-methyl-D-aspartate (NMDA) target receptor associated with a neurological disorder in a subject, and a method for modifying the function of a N-methyl-D-aspartate (NMDA) target receptor associated with a neurological disorder in the central nervous system of a subject. Each recited method comprises administering a vaccine comprising a therapeutically effective amount of an antigen (NMDAR1) wherein the antigen elicits the production of antibodies in the circulatory system of the subject, wherein the antibodies bind to a target receptor on a neuronal cell in the central nervous system and modify the function of the target receptor. The basis for this rejection is set forth for claims 1-3, 5-12, 22-32, 36-46, 54, 59-61, and 68 at pg 3-7 of the previous Office Action (Paper No. 12, 27 August 2001). Claims 70-72 and 74-76 are directed to a composition comprising a therapeutically effective amount of an NMDA antigen capable of eliciting the production of

NMDA antibodies in the circulatory system of the subject, wherein the NMDA antibodies bind to an NMDA receptor on a neuronal cell in the central nervous system of a subject, and modify the function of the NMDA receptor in the central nervous system, such that the modification of the NMDA receptor protects against a neurological disorder. The claims also recite that the antibodies cross the blood-brain barrier, the antigen is N-methyl-D-aspartate receptor subunit 1, and the target protein is an N-methyl-D-aspartate (NMDA) receptor. The basis for this rejection is set forth for originally filed claims 70-76 at pg 7-9 of the previous Office Action (Paper No. 12, 27 August 2001).

Applicant's arguments (Paper No. 15, 28 January 2002), as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Applicant asserts that the specification describes in detail how to generate antibodies against a central nervous system antigen in the systemic circulatory system of a subject, such that the antibodies migrate across the blood-brain barrier when it is compromised, and bind to a target receptor on a neuronal cell. Applicant contends that using NMDAR1 as antigen for the NMDA receptor, antibodies against the antigen were raised in rat models of neurological disorders. Applicant indicates that Example 3 demonstrates the neuroprotective effect against epilepsy using a well established and art recognized animal model for epilepsy. Applicant states that rats were vaccinated with a gene encoding an NMDAR1 antigen. Applicant indicates that circulating antibodies were produced in the circulatory system of these animals after vaccination. Applicant asserts that the circulating antibodies have a neuroprotective effect because the rats injected with the gene did not develop seizures or hippocampal injury. Furthermore, Applicant argues that the vaccine also has anti-stroke and ischemic neuroprotection efficacy, as demonstrated in Example

4. Applicant submits that the specification demonstrates the neuroprotection effect of the vaccine resulting from direct modification of the NMDA receptor using fluorescent calcium loading techniques in Example 6. Applicant indicates that circulating antibodies produced in rats vaccinated with the neuroprotective vaccine were isolated. The isolated IgG antibodies were incubated *in vitro* with cultured primary neuronal cells which express the NMDA receptor. The cultured neuronal cells treated with the isolated IgG antibodies did not display an increase in fluorescent signal compared with control cells, indicating that the IgG antibodies isolated from the NMDAR1 vaccinated animals bind to the NMDA receptor expressed in cultured neuronal cells. Additionally, Applicant argues that the circulating antibodies bind to a target receptor and modify downstream processes (indirect modification). Applicant contends that the expression of Krox-24 protein, a protein activated by the NMDA receptor, is reduced within the cortical brain regions of animals treated with the NMDA neuroprotective vaccine. Applicant also states that the specification demonstrates improved performance and improved contextual memory in NMDA vaccinated animals.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, Applicant has not provided evidence to demonstrate the modification of the function of any target receptor associated with a neurological disorder, cognition, or a neuroendocrine disorder in a subject by administration of a peptide vaccine comprising an antigen (NMDAR1). The specification teaches subcloning the full length mouse NMDAR1 cDNA into an adeno-associated virus (AAV) plasmid to yield a recombinant virus, AAVNMDAR1 (pg 54, lines 14-19). The specification also teaches the peroral administration of this vector to groups of rats (pg 54, lines 19-22; pg 59-75). The specification discloses

NMDAR1 protein expression and the presence of circulating antibodies in rats administered the genetic vaccine (pg 55-57). However, the specification provides no guidance or working examples for the administration of a NMDAR1 antigen peptide vaccine and modification of the function of any target receptor in a subject. The examples in the specification disclose the delivery of the full length mouse NMDAR1 *gene* into rats while the claims of the instant application recite the delivery of an *antigen* into a subject. The working examples in the specification directed to administration of the genetic vaccine (as reviewed in Applicant's arguments above) do not provide guidance regarding the administration of a protein vaccine to subjects. Additionally, there is no guidance or working examples in the specification to indicate that if administered, the NMDA antigen produces anti-NMDA antibodies and that the antibodies bind to a target receptor on a neuronal cell to directly modify the receptor or indirectly modify the function of a process involving the receptor *in vivo*. Example 6 in the specification only describes (i) an *in vitro* assay utilizing primary mesencephalic rat neuronal cultures and purified IgG from AAVNMDAR1 vaccinated rats and (ii) an immunohistochemistry assay of Krox-24 levels in the cortex of AAVNMDAR1 treated rats.

(ii) The specification also does not teach which specific neuronal cell(s) the target NMDA receptor is present on. Numerous types of neuronal cells are present in the central nervous system of a subject, such as dopaminergic neurons, serotonergic neurons, oligodendrocytes, Schwann cells, and astrocytes. Therefore, regarding the instant application, undue experimentation would be required of the skilled artisan to modify the function of a target receptor on any neuronal cell associated with a neurological disorder, cognition, or neuroendocrine disorder in a subject by administration of an NMDA antigen.

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(iii) Additionally, the specification does not teach "protecting against" a neurological disorder or a neuroendocrine disorder by modifying the function of a receptor in a subject. The phrase "protecting against" is interpreted as meaning that an activity will not occur, i.e. a neurological or neuroendocrine disorder will not manifest/occur. Undue experimentation would be required of the skilled artisan to determine the quantity of antigen to be administered, the best route of administration, the duration of treatment, and any possible side-effects in order to generate antibodies which bind to and modify the function of the target receptor, such that modifying the function of the target receptor protects against a neurological disorder.

(iv) Furthermore, although the state of the art at the time the application was filed demonstrates the preparation of NMDAR1 peptide or fusion proteins with NMDAR1 to generate antibodies, relevant literature indicates that numerous problems exist in regards to administering a subunit (antigen) vaccine to humans and animals. Several characteristics of an ideal vaccine, regardless of species, must include: 1) efficacy greater than 90%, 2) effective after a single dose, 3) long lived immunity, 4) effective when given orally, and 5) high safety (Babiuk, LA. *Vaccine* 17: 1587-1595, 1999). Often, when some proteins are included in a vaccine, they may be immunosuppressive, but in other cases, the immune responses to proteins may enhance the disease (Babiuk, pg 1588, col 2). Although antigen vaccines have the advantage of increased safety, their major disadvantages are their low level of immunogenicity and rapid degradation *in vivo*. The rapid degradation *in vivo* may explain the low immunogenicity, even if linked to a carrier or strong adjuvant (pg 1588, col 2; pg 1590, col 2).

(v) Applicant asserts that the specification describes how to make a construct used in the composition that includes an NMDA antigen. Applicant argues that the specification provides

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guidance for other NMDA antigens that can readily be substituted. Applicant indicates other NMDA receptor subunit families and provides a number of reference citations that the skilled artisan could use for further information.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, the specification does not teach a composition comprising any antigen, which is capable of eliciting the production of antibodies in the circulatory system of the subject. The assertion that other NMDA antigens can readily be substituted for NMDAR1 cannot be accepted in the absence of supporting evidence, because the relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities. For example, Tischer et al. (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen *in vivo*, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125:1591-1598; see Abstract and pp. 1594-1596). In the transforming growth factor (TGF) family, Vukicevic et al. (1996, PNAS USA 93:9021-9026) disclose that OP-1, a member of the TGF- β family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF- β family members BMP-2 and TGF- β 1 had no effect on metanephrogenesis under identical conditions (p. 9023, paragraph bridging columns 1-2). See also Massague, who reviews other members of the TGF- β family

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(1987, Cell 49:437-8, esp. p. 438, column 1, second full paragraph to the end). Similarly, PTH and PTHrP are two structurally closely related proteins which can have opposite effects on bone resorption (Pilbeam et al., 1993, Bone 14:717-720; see p. 717, second paragraph of Introduction). Finally, Kopchick et al. (U.S. Patent 5,350,836) disclose several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid (column 2, lines 37-48).

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only

about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

Therefore, based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan how to use other NMDA receptor subunit families without resorting to undue experimentation to determine what the specific biological activities of each family member are.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to modify the function of a target receptor associated with a neurological disorder, cognition, or neuroendocrine disorder by administration of an antigen vaccine and to determine an activity of other NMDA receptor subunit family members, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, and the unpredictability of the response and longevity of the antigen vaccine *in vivo* (see discussion and recited reference), the state of the prior art establishing that biological activity cannot be predicted based on structural similarity, and the breadth of the claims which embrace a broad

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class of structural NMDA variants, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Claim Rejections - 35 USC § 112

7. Claims 70-72 and 74-76 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 70-72 and 74-76, the acronym "NMDA" renders the claims vague and indefinite. Abbreviations should be spelled out in all independent claims for clarity.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 70-72 and 74-76 are rejected under 35 U.S.C. 102(b) as being anticipated by Luo et al. (Molec Pharmacol 51: 79-86, 1997).

Luo et al. teach a composition comprising an NMDA antigen capable of eliciting the production of NMDA antibodies in the circulatory system of a subject. Luo et al. disclose the expression of a fusion protein using a vector generated by ligating the cDNA encoding amino acids 1-561 from the NMDAR1A sequence into the BamHI site of the plasmid pET 14b. Samples are aliquoted, lyophilized, and stored until use (pg 80, ¶ 4). Luo et al. also teach that the purified protein is resuspended in either Freund's complete adjuvant or Freund's incomplete adjuvant and injected into mice (pg 80, col 1-2). Antibodies are generated and purified over an

affinity column. Please note that a compound and all of its properties are inseparable; they are one and the same thing (see *In re Papesch*, CCPA 137 USPQ 43). Simply stating a new property of the NMDAR1 antigen or antibody of Luo et al. does not render the composition comprising an NMDA antigen that elicits the production of NMDA antibodies (and wherein the NMDA antibodies bind an NMDA receptor and modify the function of the NMDA receptor such that the modification of the NMDA receptor protects against a neurological disorder) of the instant application free of the art.

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Conclusion

No claims are allowable.

The art made of record and not relied upon is considered pertinent to applicant's disclosure:

During et al. Science 287: 1453-1460, 2000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

BEB
Art Unit 1647
February 20, 2002

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER